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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,968	07/31/2003	John J. Rossi	1954-401	3645

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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
03/11/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/630,968	ROSSI ET AL.	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,17 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,17 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on November 20, 2009.

Currently, claims 1-9, 17, and 19-23 are pending and under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

Claims 1-9, 17, and 19-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Shi et al., Medina et al., and Dietz for the reasons of record as set forth in the Office action mailed on July 8, 2009 and for the reasons stated below.

Applicant's arguments filed on November 20, 2009 have been fully considered but they are not persuasive. Applicant argues that the claims are not obvious because Shi et al. taught "cloning" methods for preparing siRNA expression cassettes, not the PCR amplification-based

method claimed in the instant case. Applicant's attention is directed to the fact that the last Office action made it explicitly clear that Shi et al. taught "cloning/ligation methodologies" for producing siRNA expression cassettes, not PCR amplification-based methods. See page 5 of the last Office action dated July 8, 2009. Hence, examiner does not understand how applicant's reiteration of what was already stated in the Office action supports applicant's alleged nonobviousness of the claims. Further, in response to applicant's arguments against the references individually, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated in the last Office action, obtaining efficient methods for producing siRNA expression cassettes that contain a mammalian promoter (such as U6 or H1) and a termination signal sequence, wherein the expression cassettes successfully transcribe siRNAs in mammalian cells, was an art-recognized goal as evidenced by the teachings of Shi et al. Although the teachings of Shi et al. are limited to siRNA expression cassette (or vector) production by cloning methods, it was known in the art, as stated in the last Office action, that one can make expression vectors not only by cloning methods but also by PCR-based amplification methods as taught and suggested by Medina et al. As such, the "combination" of the cited prior art references does teach and suggest the instantly claimed PCR-based amplification method for producing an siRNA expression cassette, and furthermore, the "combination" of the cited prior art references and the state of the art/technology disclosed by the "combination" of the prior art references do indicate that the level and skill of an ordinary artisan were sufficiently advanced enough to modify the cloning-based siRNA expression cassette

production method of Shi et al., thereby allowing the artisan to successfully arrive at the PCR-based amplification production of an siRNA expression cassette.

Applicant argues that the teachings of Medina et al. do not cure the deficiency of Shi et al. because "Medina et al. does not disclose the amplification of a promoter using a primer pair as set forth in the claims, i.e., a primer complementary to the 5' end of the promoter and a primer complementary to the 3' end of the promoter." Contrary to applicant's argument, one of ordinary skill in the art knowledgeable of the teachings of Medina et al. and skilled at PCR-related techniques would have successfully identified that a primer "pair" is necessary that can effectively synthesize and amplify the promoter sequence that is operably linked to an siRNA (sense and antisense strands) sequence, when and if the artisan were to pursue PCR-based production of an siRNA expression cassette in place of the ribozyme expression cassette of Medina et al. Again, applicant's arguments are solely based on the teachings of Medina et al. alone, completely dismissing the fact that the instant rejection is based on a "combination" of prior art references. Note that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As pointed out in the last Office action, nucleic acid expression cassettes were known to be synthesizable either by cloning methodology (see Shi et al.) or PCR-based amplification methodology (see Medina et al.). As such, cloning and PCR-based amplification methodologies were recognized as functionally equivalent, interchangeable methodologies for producing a desired nucleic acid-based expression cassettes. Now, applicant's attention is directed to the fact that the structure of an siRNA expression cassette that can successfully transcribe both the sense and antisense strands of a double-stranded siRNA in a mammalian cell

was known in the art at the time of filing. In addition, nucleic acid expression cassettes comprising different promoters were known in the art. For example, Shi et al. taught a structure wherein a U6 or H1 RNA promoter is operably linked to the sense and antisense strand sequences of an siRNA, followed by a transcriptional termination signal sequence of 5 dT's; Dietz taught a structure wherein a U1 promoter operably linked to a ribozyme sequence successfully transcribes a ribozyme in a mammalian cell; and Medina et al. taught a structure wherein a T7 promoter operably linked to a ribozyme sequence. Given the wealth of knowledge disclosed by the cited prior art references, further in view of the exemplary PCR-based expression vector production method of Medina et al., it would have been apparent to a person of ordinary skill in the art that making an "siRNA" expression cassette via PCR amplification method would require a primer "pair", wherein one primer (oriented in a 5' direction, thus forward primer) must efficiently synthesize and amplify the nucleotide sequence of the promoter, and wherein the other primer (oriented in a 3' direction, thus reverse primer) must efficiently synthesize and amplify the nucleotide sequence that follows the promoter sequence: the siRNA sequence and the transcriptional termination signal sequence. That is, when modifying the ribozyme expression vector production method of Medina et al. to produce an siRNA expression vector, one of ordinary skill in the art would have used a primer that "binds at the 5' end of" (see page 1700, left column of Medina et al.) the expression cassette that contains the promoter sequence and another primer that "binds at the 3' end of" (see page 1700, left column of Medina et al.) the expression cassette that contains the siRNA sequence and also "binds downstream of" (see page 1700, left column of Medina et al.) the siRNA sequence. Furthermore, when designing the "reverse" primer or the primer that binds at the 3' end of the expression cassette, it would have been apparent to one of ordinary skill in the art that the "reverse" primer must also include

a nucleotide sequence that binds at the 3' end of the U6 or H1 promoter sequence because U6 or H1 or U1 promoter sequence is much longer than the T7 promoter sequence disclosed in Medina et al. Note that the T7 promoter sequence is 5'-TAATACGACTCACTATAGGG-3', thus only 20 nucleotides in length. See page 1700 of Medina et al. In contrast, the mammalian U6 promoter or H1 promoter sequence, for example, is longer than 300 nucleotides in length. See Figure 1A; paragraphs 0079-0080, and SEQ ID NOs:3-5 of Shi et al. Note that the human U6 promoter sequence is 464 nucleotides in length and the human H1 promoter sequence is 497 nucleotides in length. Hence, it would have been apparent to one of ordinary skill in the art to include a nucleotide sequence that is complementary to and binds/hybridizes to the 3' sequence of the U6 or H1 promoter sequence along with the siRNA sequence and the termination signal sequence when designing the reverse primer, so as to successfully produce an siRNA expression cassette containing the full-length U6 or H1 promoter that is operably linked to the siRNA sequence, thereby successfully transcribing the siRNA in a mammalian cell. That is, the mere fact that Medina et al. did not teach using a reverse primer that binds to the 3' of the promoter sequence for producing a T7 promoter-containing expression cassette does not render the claims any more patentable or nonobvious because the instant rejection is based on a "combination" of prior art references and the technology disclosed by the references, wherein it would have been obvious to and within the technical grasp of a person of ordinary skill in the art that a 3' reverse primer sequence, which is not only complementary to the siRNA and termination signal sequences but also complementary to the 3' region of the U6 or H1 promoter sequence, is necessary in order to produce an siRNA expression vector containing a U6 or H1 promoter sequence that ranges about 300-500 nucleotides in length.

Applicant argues that the claims are not obvious because Dietz et al. do not teach an amplification method as claimed. Again, in response to applicant's arguments against the references individually, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated hereinabove and in the last Office action, the instant rejection is based on a combination of Shi et al., Medina et al., and Dietz, wherein the combined teachings of the cited prior art references and the state of the art/technology disclosed by the references render the claims obvious.

Since applicant's arguments do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited, this rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi (Acting SPE) can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

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Examiner, Art Unit 1635